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Title: Syndromes of Hypercoagulability: Protein C and Protein S Deficiencies

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Imagine that you are receiving report from the night shift nurse. You are assigned a 41-year-old Caucasian female who was admitted with a second stroke. You note that the patient smoked one pack of cigarettes per day and has no history of coronary artery disease, hypertension, valvular disease, atrial fibrillation, or deep vein thrombosis. The neurologist described her condition as thrombotic strokes from an unknown origin. All routine diagnostic procedures were negative for a cerebral bleed. Your patient is on intravenous heparin, enteral feedings, and mechanical ventilation through a tracheostomy tube. Cardiac monitoring shows normal sinus rhythm. You learn that the patient is unable to move her left extremities and has a weak right hand grip. The night shift nurse concludes report by saying that a geneticist will meet with the family because the neurologist believes that the strokes were caused by a hereditary, hypercoagulable defect.

When reading the patient's chart you notice that prior to admission, your patient was active and healthy, despite a previous stroke 2 years ago. According to her family, her only residual deficit was a barely noticeable fine motor weakness of her left hand. She independently cared for her two teenage children. Later, the geneticist and neurologist inform the patient's family that she has been diagnosed with Protein C and Protein S deficiencies. The neurologist briefly explains that this disorder makes her "throw clots" and recommends that the entire family be tested for these deficiencies. After the meeting, the family turns to you for further explanations. You feel a sense of dread because you are unfamiliar with Protein C and Protein S deficiencies.

Proteins C and S are vitamin K-dependent factors which are synthesized in the liver. Protein C and Protein S deficiencies upset the normal hemostatic balance in favor

of thrombosis. This article reviews Protein C and Protein S deficiencies, including diagnosis, clinical manifestations, and treatment. Clinicians who recognize Protein C and Protein S deficiencies can improve patient outcomes and survival rates.

Scope of the Problem

Thrombosis is the leading cause of death in the United States.¹ Approximately two million people die from consequences of arterial or venous thrombosis annually. Over 50% of these victims have an inherited or acquired blood coagulation protein defect or platelet defect that predisposes them to hypercoagulability and thrombosis.¹ The scope of thrombosis and its consequences are manifested as deep vein thrombosis (DVT), pulmonary embolus (PE), acute myocardial infarction (AMI), cardiovascular thrombosis, retinal thrombosis, and fetal wastage syndrome (see table 1).¹

Blood coagulation is a complex system involving many genes, clotting factors, and tissues. There are a number of gene mutations which promote the development of thrombi. Clinicians are now able to identify many of the gene-gene interactions that result in genetically transmitted predisposition to thrombosis.² Inherited predispositions to thrombosis are disturbing to clinicians because they frequently affect young patients.

History

The role of coagulation protein defects in the development of hypercoagulability was not well defined until the early 1980s when Protein C and Protein S were "rediscovered" as causes of inherited thrombophilia.¹ In 1976, Stenflow isolated Protein C in "pool C" of a laboratory analysis he was conducting, thus the name Protein C.³ The

following year, DiScipio discovered Protein S in Seattle, thus the name Protein S, as a Vitamin K dependent co-factor for Protein C inactivation of factor Va.^{1,3}

During the last 20 years, approximately 15 blood coagulation protein and platelet defects that predispose patients to hypercoagulability have been identified.^{1,3} The common and uncommon defects of blood coagulation are listed in Table 2. Deficiencies of Protein C and Protein S are only two of many possible combinations of coagulation defects.

Pathophysiology

Coagulation exists as a fragile balance between procoagulant and anticoagulant factors. Normal clot formation and clot lysis is a continuous process. Deficiencies in anticoagulant factors may lead to hypercoagulability and thrombosis.

Over 150 years ago, German pathologist, Virchow, identified three factors present in the development of thrombosis: stasis of blood, changes in the vessel wall, and changes in the composition of the blood. Risk factors, such as hyperlipidemia, obesity, immobility, tobacco use, and estrogen therapy, paired with an inherited or acquired predisposition to hypercoagulability, may be a fatal combination.¹

Coagulation disorders are characterized as inherited or acquired disorders (see table 3).⁴ Inherited deficiencies of blood coagulation proteins rarely cause disease on their own. However, the genetic predisposition to hypercoagulability, combined with other risk factors or disease states, may lead to thrombosis and its sequelae.^{4,5}

Protein C requires the presence of Protein S to exert its inhibition effect. Combined deficiencies of Protein C and Protein S cause uninhibited factor Va and VIIIa

to actively promote coagulation. Protein C and Protein S deficiencies are inherited independently of one another. Both are autosomal dominant traits with large variability in transfer of the trait to their offspring. A large number of symptomatic and asymptomatic mutations occur in transmission of Protein C deficiency which are manifested in a wide variety of symptoms.^{3, 6} Homozygous Protein C deficiency patients (patients who inherited the trait from both parents) have almost no Protein C and develop thromboembolic complications as a neonate. Heterozygous patients (patients who inherited the trait from one parent) may be asymptomatic, but are at increased risk of developing thromboembolic diseases at an early age.⁷

Protein S is produced primarily by hepatocytes but is also detected in endothelial cells and platelets.⁵ Acquired decreases in levels of Protein S are caused by warfarin therapy, type I diabetes, nephrotic syndrome, estrogen therapy, oral contraceptives, and illnesses, such as disseminated intravascular coagulation (DIC), that activate the procoagulant system.¹

Thrombi may originate in arteries or veins. Patients with venous thrombosis have a 2-5% incidence of Protein C deficiency and a 5-10% incidence of Protein S deficiency.^{5, 7}

Clinicians should suspect a defect of blood coagulation proteins in patients who present with a family history of thrombosis, thrombosis at an early age, recurrent thrombosis without obvious precipitating factors, warfarin-induced skin necrosis, or recurrent thrombosis despite anticoagulant therapy. Additionally, because cerebral, hepatic, mesentery, axillary vein, and sagittal sinus thromboses are unusual, these should raise suspicion of hypercoagulable disorders.^{5, 7}

Clinical manifestations of Protein C deficiencies

Common manifestations of Protein C deficiencies are purpura fulminans, venous thrombosis, and/or PE. Superficial thrombophlebitis is also a common manifestation, whereas, arterial thrombosis is rare with Protein C deficiencies.⁸

Acquired Protein C deficiencies are often found post-operatively and in patients with major illnesses such as acute respiratory distress syndrome, DIC, extensive DVT, malignancy, severe liver disease, and sepsis.⁹ L-asparaginase therapy (used in malignant lymphoblastic leukemia) also decreases the production of coagulation factors, including Protein C and Protein S.¹⁰ Additionally, critically ill patients are predisposed to clotting related to venous access devices, prolonged bed rest, poor nutrition, and infections.

Diagnosis of Protein C deficiencies

Recent advances in technology make diagnosis of blood coagulation protein disorders more accurate. Levels of circulating protein as well as immunoassay identification of phenotypes are now available. Protein C has a half-life of approximately 8 hours; its plasma concentration is 4 mg/l.¹¹ Patients with Protein C concentrations below 70% may have a hereditary deficiency. Values between 55% and 70% are considered borderline.^{3, 11}

It remains difficult to test for Protein C and Protein S deficiencies and establish normal ranges because levels of these proteins decrease during acute illness. It is best to test patients in a non-acute thrombotic state and while they are off anticoagulants. This testing is difficult to accomplish during the intensive care phase of critical illness. The

actual diagnosis of the blood coagulation protein defect may not take place until the patient recovers from the first thromboembolic event and is managed at home for several months on anticoagulant therapy.

Recent immunoenzymatic assay measurements reveal two types of Protein C deficiency. Type I, the most common form, is due to reduced synthesis of the normal protein resulting in low plasma concentrations. Type II is characterized by normal synthesis of a protein that is not functional.

A thorough noninvasive evaluation of the heart and aorta, as well as other potential sites of thromboembolism, should be included in the diagnostic evaluation of the patient. Mesenteric and cerebral arterial vascular beds are frequently affected by arterial thromboses related to inherited coagulation defects.¹²

Treatment of Protein C deficiencies

The treatment of the critically ill patient varies greatly based on the organ systems involved and the severity of the thrombosis. A major goal is to prevent organ failure related to thromboses. Acute thrombosis is treated with intravenous heparin or low-molecular-weight heparin injections in combination with warfarin until the prothrombin time (PT) is therapeutic, a process that takes four to five days. Recommended PT and International Normalized Ratio (INR) values are very similar to standard anticoagulation, a PT of 2 to 2.5 times the control and an INR of 2.0 to 3.0.^{5, 12} Warfarin should be continued for about three to four months. Infusions of fresh frozen plasma and factor IX concentrates provide abundant amounts of Protein C for homozygous patients with very

low levels of Protein C.⁹ Intravenous Protein C concentrate may be beneficial, however, it is not yet widely available.^{13, 14}

For acquired deficiencies, the underlying cause needs to be identified and treated before significant improvement can be expected. Once the underlying disease process is stabilized, long-term therapy is considered.

The difficult decisions about long-term anticoagulant therapy are made based on several factors: the numbers of sites involved, the severity of the event, and whether the event was spontaneous or secondary to other conditions.⁹ The practitioner needs to carefully weigh the risk of recurrent thrombosis against the complications of long-term anticoagulation.

Clinical Manifestations of Protein S deficiencies

Similar to Protein C, Protein S deficiencies often present as thrombosis in patients less than 40 years of age, recurrent thrombosis without obvious risk factors, warfarin-induced skin necrosis, cerebrovascular accident (CVA), or thrombosis at an unusual site.^{5,}
⁹ Homozygous patients may be severely affected, may die in utero, or may develop purpura fulminans shortly after birth. Heterozygous patients' symptoms vary greatly from being asymptomatic to DVT and PE that begin in the late teens. Warfarin-induced skin necrosis and arterial thromboembolic events are more common with inherited Protein S deficiencies than in Protein C deficiencies.^{1, 11}

Diagnosis of Protein S Deficiencies

Immunoenzymatic assays have identified three types of Protein S deficiencies. Type I deficiency results from an insufficient amount of total and free Protein S. In Type II deficiency, Protein S is at a normal level, but malfunctions due to low Protein C cofactor activity. Type III deficiency is characterized by low free Protein S levels but normal total Protein S levels. Normal ranges vary greatly with age and gender.⁷ Protein S levels below 55% indicate a deficiency.^{5, 11, 12}

Health care providers need to recognize that levels of Protein C and Protein S decrease to about 40 to 60% of normal within 48 hours of starting warfarin therapy. These levels will return to normal after about two weeks of warfarin therapy so assays may be drawn at this time. Once safely anticoagulated and managed without recurrent thrombosis for several months, the patient may be taken off warfarin and placed on low-molecular-weight heparin to facilitate accurate testing.^{4, 5, 7}

The diagnosis of Protein S and Protein C deficiencies is complicated and costly, approximately \$1,400 to \$1,700.^{4, 15} Although debate continues, experts generally agree that testing should also be offered to those with thrombosis at an unusual site and for patients who presented with a life-threatening event.^{7, 15} Testing of asymptomatic family members remains controversial due to the expense and complexity of the process.

Treatment of Protein S deficiencies

The treatment of Protein S deficiencies is similar to treatment of Protein C deficiency. The goals are to prevent organ dysfunction and to identify and treat blood coagulation protein defects while modifying life style habits that promote thrombosis.

Heparin or low-molecular-weight heparin is used in the acute setting until the patient is hemodynamically stable. Overlap with warfarin should begin at low doses to prevent warfarin-induced skin necrosis. Commercial concentrates have been used with success in homozygous infants and a few severely affected adults.^{8, 10, 14, 16}

As with Protein C, the decisions about long-term management are difficult. Protein S deficiency may predispose the patient to an even higher risk of cardiovascular thromboembolic events, so life-long anticoagulation may be considered.⁵

Activated Protein C Resistance

In 1993, an additional inherited hypercoagulable defect was identified as activated Protein C resistance.^{3, 16} This abnormality causes factor Va to be resistant to inhibition by activated Protein C. Recent studies have revealed that activated Protein C resistance is more prevalent than Protein C and Protein S deficiencies.^{8, 14, 17} Activated Protein C resistance affects 4% to 8% of the general population and approximately 30% to 40% of patients with thromboembolism.¹⁷ Approximately 10% of patients with Protein C deficiencies will also have activated Protein C resistance.³ The presentation and clinical manifestations of activated Protein C resistance are similar to deficiencies of Protein C and Protein S. Treatment is also comparable, with use of anticoagulant therapy and careful monitoring.

Nursing Implications for Protein C and Protein S deficiencies

Awareness of blood coagulation defects and their consequences enhances the nurse's knowledge in management of critically ill patients. The nurse is often the one to

recognize the complications of acute illness and prompt the care provider to investigate further through consultation with hematology experts and further diagnostic testing.

Once the acutely ill patient is stabilized, the nurse assumes additional roles of advocacy and education. Referrals for genetic counseling and testing should be offered to patients and family members at risk for thrombosis. Patients and family members should also be taught about risk factors for hypercoagulability, such as obesity, oral contraceptive and estrogen use, immobility, surgery, trauma, and pregnancy. Patients and family members should also be informed of habits that predispose them to thrombotic events such as a sedentary life-style, prolonged sitting or standing, crossing of the legs, pressure under the knees, wearing restrictive clothing, and tobacco use. Effective management may include prophylactic use of anticoagulation during high-risk clinical situations such as pregnancy, immobility, or perioperative states.¹

Patients and family members should be taught the signs and symptoms of deep vein thrombosis, including swelling of extremities, prominent superficial veins, skin lesions, and pain, especially if unilateral and sudden. Patients and family members should be informed of other signs of thromboembolism that need immediate medical attention such as headache, abdominal pain, sudden chest pain, shortness of breath, and convulsions.¹⁸

Patients receiving anticoagulant therapy should be taught to observe for complications such as hematuria, melanic stools, bleeding gums, epistaxis, skin necrosis, and excessive bruising. They should also be counseled regarding close PT and INR monitoring and the importance of compliance with follow-up appointments with their care provider.

Summary

Thromboembolism often results from a combination of inherited or acquired defects of coagulation proteins, such as Protein C and Protein S, combined with risk factors that predispose patients to hypercoagulability.¹⁶ Nurses have an important role in recognizing and preventing thromboembolic events. Awareness of these unusual blood coagulation protein defects may prompt further investigation and prevent multisystem complications. Diagnosis and treatment with anticoagulants may prevent further thromboembolic events as the patient recovers from critical illness. Prior to discharge, the patient and family should be encouraged to partner with their care provider to carefully manage the disorder and prevent potentially devastating complications.

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Table 1. Scope of thrombosis and its consequences

Disorder	Percent Related to a Coagulation Defect or Platelet Disorder
Deep Vein Thrombosis	30-50%
Pulmonary Embolus	30-50%
Acute Myocardial Infarction	50%
Cardiovascular Thrombosis	30%
Retinal Arterial or Venous Thrombosis	30%
Fetal Wastage Syndrome (miscarriage)	30-50%

Source: Bick RL, Kaplan H. Syndromes of thrombosis and hypercoagulability: congenital and acquired causes of thrombosis. *Medical Clinical of North America* 1998;82(3):409-58.

Table 2. Common and uncommon defects of blood coagulation proteins and platelet defects

Common Defects	Uncommon Defects
Antiphospholipid syndrome	Tissue plasminogen activator defects
Activated Protein C Resistance (Factor V Leiden)	Plasminogen activator inhibitor defects
Sticky platelet syndrome	Plasminogen defects
Protein C defects	Heparin cofactor II defects
Protein S defects	Wein-Penzing defect
Antithrombin defects	Dysfibrinogenemia
Prothrombin 20210A	Homocysteinemia
	Lipoprotein A

Source: Bick RL, Kaplan H. Syndromes of thrombosis and hypercoagulability: congenital and acquired causes of thrombosis. *Medical Clinical of North America* 1998;82(3):409-58.

Table 3. Inherited versus acquired defects that predispose patients to hypercoagulability

Inherited	Acquired
Activated Protein C resistance	Antiphospholipid syndrome
Protein S deficiency	Hyperhomocysteinemia
Protein C deficiency	Thrombocytopenia
Antithrombin deficiency	Dysproteinemia
Hyperhomocysteinemia	Heparin induced thrombocytopenia
Prothrombin 20210A allele	Estrogens – birth control pills and hormone replacement therapy
Dysplasminogenemia	Acquired Protein C deficiency
High plasminogen activator inhibitor	Acquired Protein S deficiency
Dysfibrinogenemia	
Elevated factor VIII	

Source: Abramson N, Abramson S. Hypercoagulability: clinical assessment and treatment. *Southern Medical Journal* 2001;94(10):1013-20.